6. (Twice Amended) A method according to Claim 1, wherein said moiety specific for a surface protein is a [low molecular weight binding molecule, wherein said] small organic molecule having a molecular weight [is] of more than 100 and less than about 5000 daltons.

Please cancel Claim 12 without prejudice or disclaimer.

REMARKS

Claims 1-13 were pending for prosecution in the present application. Applicants have herein canceled Claim 12, thereby leaving Claims 1-11 and 13 pending for prosecution herein.

Support for various amendments to the claims can be found in the specification at least as follows:

Claim 1 - for "ligand for a receptor" at page 6, lines 7-8;

Claim 2 - for "antigen to which the host has been previously sensitized" at page 7, lines 25-26; and

Claim 6 - for "small organic molecule" at page 6, line 23.

The Obviousness-Type Double Patenting Rejections

Claims 1-3 and 5-8 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 1-5 of copending application Serial No. 07/690,530. Claim 4 stands provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims

1, 4 and 5 of copending application Serial No. 07/690,530 in view of the art discussed in the specification at page 9, first paragraph. Claim 12 stands provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 6-8 of copending application Serial No. 07/690,530 in view of Lorberboum-Galski et al. Claims 9-11 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 1, 2, 4 and 5 of copending application Serial No. 07/690,530. Claims 1-3 and 5-11 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 9-10 of copending application Serial No. 07/690,530. Claim 12 stands provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 9-10 of copending application Serial No. 07/690,530. Finally, Claims 9-11 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 6-8 of copending application Serial No. 07/690,530.

In response, Applicants would be willing to submit an appropriate terminal disclaimer to obviate the outstanding provisional rejections. Applicants wish, however, to withhold the preparation and filing of such a terminal disclaimer until there is an indication from the Examiner of otherwise allowable subject matter.

Claims 1-13 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable

over Claims 1-7, 11 and 12 of copending application Serial No. 08/254,299.Also, Claims 1-8, 12 and 13 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 8-10 of copending application Serial No. 08/254,299.

In response, Applicants notes that prior application Serial No. 08/254,299 has now been officially abandoned, thereby obviating these provisional rejections.

The Rejections under 35 U.S.C. § 101

Claims 9-11 stand provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as that of Claims 8-10 of copending application Serial No. 08/254,299. However, since prior application Serial No. 08/254,299 has now been officially abandoned, this rejection is now moot.

The Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-13 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which is not described in such a way as to enable one skilled in the art to which it pertains to make and use the claimed invention. Specifically, the Examiner asserts that notwithstanding that Applicants have demonstrated utility of the claimed invention both (1) *in vitro* and (2) *in vivo* in mice, the specification does not disclose how to use the claimed invention for the treatment of disease in humans. Applicants respectfully traverse the rejection.

Prior to addressing the substantive rejection, Applicants believe that a brief summary of th experimental results presented in the present application will prove helpful. In Example 1 on pages 12-14 of the specification, Applicants clearly demonstrate that a conjugate comprising a blood group A synthetic trisaccharide antigen linked to interleukin-2 is capable of binding *in vitro* to lymphocytes expressing a high affinity interleukin-2 receptor and killing those cells through antibody-dependent cell lysis. These results provide clear and unambiguous *in vitro* support for the presently claimed invention.

In Example 2 on pages 14-17 of the specification, Applicants clearly demonstrate that a conjugate comprising a hepatitis B surface antigen linked to interleukin-2 is capable of binding *in vitro* to lymphocytes expressing a high affinity interleukin-2 receptor and killing those cells through antibody-dependent cell lysis. These results also provide clear and unambiguous *in vitro* support for the presently claimed invention.

In Example 3 on pages 17-18 of the specification, Applicants clearly demonstrate that a conjugate comprising an α-Gal antigen linked to folate is capable of binding *in vitro* to tumor cells expressing a high affinity folate receptor and killing those cells through anti-α-Gal antibody-dependent cell lysis. These results again provide clear and unambiguous *in vitro* support for the presently claimed invention.

In Example 4 on pages 18-25 of the specification, Applicants clearly demonstrate that a conjugate comprising an $F(ab')_2$ fragment of polyclonal anti-thymocyte gl bulin (ATG) is bound to fluorescein isothiocyanate (FITC) is capable of binding *in vivo* to circulating T-cells in mice and killing those cells

through antibody-dependent cell lysis. These results also provide clear and unambiguous *in vivo* support for the presently claimed invention.

In Example 5 on pages 25-31 of the specification, Applicants clearly demonstrate that a conjugate comprising FITC linked to interleukin-2 is capable of binding *in vivo* to $CD25^+$ T-cells and, thereby resulting in prolonged heterotopic cardiac graft survival. These results also provide clear and unambiguous *in vivo* support for the presently claimed invention.

With regard to the present rejection, although the Examiner asserts that the claims are not enabled for the therapeutic treatment of humans, Applicants note that the pending claims are not limited to the therapeutic treatment of humans. To the contrary, the pending claims recite a method for killing a target cell in a mammalian host. As described above, Applicants have provided detailed, clear and unambiguous experimental evidence that demonstrates the utility of the claimed invention *in vivo* in mammals as presently claimed.

Essentially, the Examiner is refusing to accept the detailed, clear and unambiguous *in vitro* and *in vivo* experimental support provided in the specification as enabling for human utility. In fact, by refusing to accept the *in vitro* and *in vivo* data presented in the specification as predictive of *in vivo* utility in humans, the Examiner is apparently requiring the Applicants to provide *in vivo* data from clinical trials in humans before a patent can be issued on the claimed invention. Applicants submit, however, that this requirement is quite unreasonable, especially given the Patent Office examination guidelines (and the legal analysis supporting those guidelines) with regard to the "utility" and "how

to use" requirements of 35 U.S.C. §§ 101 and 112, first paragraph, respectively (se MPEP §§ 706.03(a)(1) and 2107.01-2107.03).

First, the examination guidelines referred to above clearly indicate that they apply to rejections both for lack of utility under 35 U.S.C. § 101 and for failing to teach "how to use" for *in vivo* therapeutic or pharmacological utility under 35 U.S.C. § 112, first paragraph. As such, these guidelines are directly applicable to the present issue.

With regard to rejections based on lack of utility under § 101 or the "how to use" requirement of § 112, first paragraph, the guidelines specifically indicate that a rejection is proper only in the "rare instance"where an assertion of specific utility for the invention made by an applicant is not credible to one of ordinary skill in the art (see MPEP § 2107). Thus, the Examiner is asserting that notwithstanding the experimental data presented in the specification demonstrating that the invention functions effectively both *in vitro* and in an *in vivo* animal model, one of ordinary skill in the art would not view an assertion of utility in humans as "credible".

Furthermore, the examination guidelines indicate that a specific assertion of therapeutic utility not only creates a presumption of utility but also is considered to be credible "unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion" (see MPEP § 2107.01(c)). Thus, since Applicants have herein asserted that the claimed invention would have therapeutic utility in humans, the presumption in favor of the Applicants can only be overcome if the Examiner demonstrates that the logic underlying

this assertion is "seriously flawed" or if the assertion of therapeutic utility is "inconsistent with th logic underlying the assertion of utility". Applicants believe that the Examiner has met neither of these requirements.

In this regard, Applicants respectfully submit that the assertion of *in vivo* therapeutic utility and efficacy herein is "credible" in light of the fact that the specification provides detailed experimental evidence demonstrating that the claimed invention works effective both *in vitro* and in an *in vivo* animal model. Thus, the logic underlying the assertion of therapeutic utility herein is neither seriously flawed nor is it inconsistent with the assertion. As such, under the PTO examination guidelines, the present rejection is improper and should be withdrawn.

Based upon the above discussion, Applicants submit that (a) the logic underlying the assertion of therapeutic efficacy in the present application is not seriously flawed and (b) the facts upon which the assertion of therapeutic efficacy is based are not inconsistent with the logic underlying the assertion. As such, under the PTO examination guidelines set forth in MPEP §§ 706.03(a)(1) and 2107.01-2107.03, the outstanding rejection is improper and should be withdrawn.

In further regard to the present rejection, however, the Examiner is also respectfully directed to Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985) where the Federal Circuit commented on the significance of data from *in vitro* testing that demonstrated how to use the invention for a practical utility. For example, the Federal Circuit stated:

> "[w]e perceive no insurmountable difficulty, under appropriate circumstances, in finding that th first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshall resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility."

Thus, under Cross, the *in vitro* demonstration of therapeutic utility for the presently claimed invention (even without the *in vivo* showing also presented in the specification) should be sufficient to obviate the outstanding rejection.

Finally, the Examiner is respectfully directed to MPEP § 2107.02(c) which discusses the "utility" requirement with regard to *in vitro* experimental data and the requirement for human clinical data showing therapeutic efficacy. Specifically, this section states:

> "if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays....almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. In no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials." (Emphasis supplied).

In fact, it is further discussed in MPEP § 2107.02(d) that primary responsibility for determining the existence of a therapeutic or pharmacological utility for a compound, composition or method in humans lies with those who are "especially skilled in the art" at the U.S. Food and Drug Administration, not with the U.S. Patent Office. As such, the new examination guidelines clearly indicate a strong preference for accepting *in vitro* data as correlative for *in vivo* efficacy. Additionally, the guidelines clearly evidence that it is a very rare instance indeed where actual human clinical trial data is required to support a claim to th rapeutic utility in humans, especially in light of the presentation in

the specification of clear and convincing *in vitro* and *in vivo* exp rimental evidence supporting the invention.

In the present Office Action at page 5, second paragraph, the Examiner states:

> "[r]egarding the mouse data disclosed in page 23 of the specification, said experiments relate to the lysis of normal cells and provide no evidence that the instant invention can be used for the treatment of any mouse disease."

Applicants, however, find the Examiner's statement to be irrelevant to the issue at hand. The present claims are <u>not</u> directed to methods for the treatment of disease as is implied by the Examiner, but rather are directed to methods for killing a target cell in a mammalian host. The experimental evidence presented in the specification clearly demonstrates what is claimed, regardless of whether is demonstrates that one can treat a disease using the method.

The Examiner's arguments regarding the Tuveson et al., Osband et al. and Borrebaeck et al. articles are also misplaced because the present claims are not explicitly directed to methods for treating a human, but rather are directed to methods for killing a target cell in a mammalian host. There is nothing in the Tuveson et al., Osband et al. or Borrebaeck et al. articles which teaches, suggests or even contemplates that a showing that the claimed invention is capable of killing target cells in a mouse is not predictive of whether the claimed method will also function to kill such target cells in humans. The Tuveson et al., Osband et al. and Borrebaeck et al. articles are all directed to an alleged lack of compatibility between mice and humans with regard to

immunotherapy and therapeutic treatment methods. As described above, however, that is not what is being claimed her in.

At page 6, lines 18-20 of the present Office Action, the Examiner further states:

> "[t]he issue at hand is not whether the rodent model is used to screen for immunosuppressive drugs, but whether the rodent model is predictive in itself of whether an agent can be used in vivo for the treatment of human disease." (Emphasis supplied).

Again, however, the Examiner comments are misplaced. The real issue at hand is, given the unambiguous experimental data in the specification demonstrating that the claimed invention is capable of killing target cells both *in vitro* and in an *in vivo* animal model, whether one of ordinary skill in the art would expect that the claimed invention could be used to kill such target cells in humans. The Examiner has provided no reasoning that would affect the credibility of the assertion made herein. Again, methods for treating a human disease are not being claimed herein.

Finally, the Examiner's comments regarding the Waldmann et al. article are also misplaced because that article, like the earlier Tuveson et al., Osband et al. and Borrebaeck et al. articles, is directed toward an allegedly lack of predictability between mice and humans when it comes to methods for therapeutically treating a human. Again, such methods are not explicitly claimed herein.

In light of the above, Applicants respectfully request that the Examiner take a fr sh look at the present rejection and reconsider the propriety of that

rejection. Applicants believe that the rejection should be withdrawn and such act is respectfully requested.

The Rejections under 35 U.S.C. § 102

Claims 1, 5 and 6 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Segal et al. as evidenced by Roitt and Rosen et al. In support, the Examiner asserts that although present Claim 1 makes clear that the moiety that binds to the cell surface is "other than an antibody", Segal et al. teach that antibody fragments may be employed, thereby allegedly reading upon the presently rejected claims.

In this regard, Applicants respectfully submit that the term "antibody" is generally employed in the art to encompass all different kinds and types of immunoglobulin molecules, including fragments of those immunoglobulin molecules which retain the ability to bind to a specific antigenic epitope. As such, when Claim 1 recites that the moiety that binds to the cell surface is "other than an antibody", one skilled in the art would understand that to mean that the moiety is not an antibody or a fragment thereof which retains its ability to recognize and bind to its specific antigenic epitope.

Be that as it may and in the interest of expediting the allowance of the present application, Applicants have herein amended Claim 1 to recite that the moiety that binds to the cell surface is other than an antibody "or fragment thereof". Since the Segal et al. disclosure teaches heteroconjugate antibodies which bind to the surface of cells wherein the antibodies of the heteroconjugates may also be fragments of antibodies which retain the ability

to bind to a cell surface antigen, the herein claimed subj ct matter is not anticipated by the Segal et al. disclosure.

In light of these remarks and the above described claim amendment, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection under 35 U.S.C. § 102(b).

Claims 1-6 and 12 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Pouletty et al. Specifically, the Examiner states that although the Pouletty et al. disclosure is essentially identical to the disclosure of grandparent application Serial No. 07/690,530 (the "'530" application) to which the present application claims priority, the claims of the present application are not entitled to priority of the earlier '530 grandparent application and, therefore, the Pouletty et al. disclosure constitutes valid prior art against the present application.

Specifically, the Examiner first states that the specification of the '530 grandparent application does not provide support for "ligands" as recited in proviso (b) of Claim 1, but rather provides support only for the term "ligands for receptors".

In this regard, Applicants respectfully submit that those of ordinary skill in the art understand that the term "ligand" denotes a molecule which is bound by another molecule, wherein the molecule that binds to the ligand is a "receptor" for that ligand. Thus, when one makes reference to a "ligand", that term automatically implies the existence of a "receptor" molecule for that ligand. In oth r words, the terms "ligands" and "ligands for receptors" are equivalent in scope and are used interchangeably by those of ordinary skill in the art.

The Examin r implies, however, that the term "ligand" as appearing in present Claim 1 is somehow not equivalent in scope to the term "ligands for receptors" as recited in the '530 grandparent application, thereby allegedly evidencing that the '530 grandparent application does not provide adequate support for the term "ligand" as it appears in present Claim 1. Notwithstanding Applicants' disagreement with the Examiner on this point, however, Applicants have herein amended Claim 1 to recite that the moiety specific for a surface protein is a "ligand for a receptor". This amendment is made simply to expedite the allowance of the present application and is not intended to affect the scope of the claim in any way (because, as described above, Applicants believe that the terms "ligand" and "ligand for a receptor" are coextensive in scope).

In that page 4, line 7, of the specification of the '530 grandparent application provides explicit support for the term "ligand for a receptor", Applicants believe that this subject matter is entitled to the priority filing date of the '530 grandparent application.

The Examiner next asserts that the '530 grandparent application does not provide support for the phrase "an antigen foreign to said mammalian host to which antibodies are present". Without agreeing with the propriety of the rejection, Applicants have amended Claim 2 to recite that the selective moiety may be "an antigen to which the host has been previously sensitized". Since explicit support for this phrase can be found in the '530 grandparent application at page 4, lines 30-32, this subject matter is entitled to the priority filing date of that grandparent application.

The Examiner next asserts that the '530 grandparent application does not provide adequate support for the phrase "low molecular weight binding molecule, wherein said molecular weight is more than 100 and less than about 5000 daltons" as recited in Claim 6. Applicants note that Claim 6 has been amended herein to recite that the moiety specific for a surface protein is a "small organic molecule having a molecular weight of more than 100 and less than about 5000 daltons".

As to whether the specification of the '530 grandparent application provides adequate support for this term, Applicants note that the specification of the '530 grandparent application at page 4, lines 1-22, provides a long list of many different possible moieties that are specific for a cell surface protein and which may be employed in the presently claimed conjugates. As one of ordinary skill in the art would be well aware, many of these moieties would fall within the range of molecular weights recited in present Claim 6, thereby providing adequate written support for the offending phrase in Claim 6.

In this regard, Applicants respectfully direct the Examiner to In re Ahlbrecht, 168 USPQ 293 (CCPA 1971) wherein the CCPA held that for a patent application to receive the benefit of an earlier filing date under 35 U.S.C. § 120, the invention claimed in that application must have been disclosed in a parent application in a manner sufficient to comply with the requirements of 35 U.S.C. 112, first paragraph. This requires that the parent application sets forth a sufficient written description of the invention to enable any person skilled in the art to make and use the invention. (Ahlbrecht at page 296). However, case law makes it abundantly clear that the claimed subject matter need not be

described literally, xplicitly or *in haec verba* in the parent application for that claimed subject matter to be entitled to priority under 35 U.S.C. § 120. (In re Lukach, 169 USPQ 795 (CCPA 1971)). To the contrary, all that is required for an earlier patent application to provide adequate written support for an invention claimed in a later patent application is that the earlier application "convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that the applicant has invented the specific subject matter later claimed" (In re Wertheim, 191 USPQ 90, 97 (CCPA 1976)).

Clearly, given the list of possible moieties set forth on page 4, lines 1-22, of the '530 grandparent application, it is clear that the inventors had invented the use of lower molecular weight binding molecules within the range of 100 to 5000 daltons and such is clearly conveyed to the ordinary skilled artisan. Therefore, Applicants believe that the presently claimed subject matter is entitled to an effective priority filing date of the '530 grandparent application.

The Examiner next concludes that the "SEB" superantigen recited in Claim 3 is not explicitly supported by the disclosure of the '530 grandparent application. Without necessarily agreeing with the propriety of the Examiner's reasoning, Applicants have herein deleted the term "SEB" from present Claim 3.

Finally, the Examiner asserts that the '530 grandparent application does not support the phrase "an immunoglobulin fragment specific for a surface membrane protein of a T cell" as recited in Claim 12. Without necessarily agreeing with the propriety of the Examiner's conclusion, Applicants have herein canceled Claim 12, thereby rendering this issue moot.

In light of the above, Applicants respectfully submit that the invention as now claimed in Claims 1-6 is fully supported by the specification of the '530 grandparent application and is, therefore, entitled to an effective priority filing date of April 23, 1991. As such, since the Pouletty et al. reference is published one year after this effective priority filing date, Pouletty et al. is not valid prior art under 35 U.S.C. § 102(b). Applicants, therefore, respectfully request reconsideration and withdrawal of the outstanding rejection under 35 U.S.C. § 102.

The Rejection under 35 U.S.C. § 103

Claim 4 remains rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Pouletty et al. Applicants respectfully traverse the rejection.

In this regard, Applicants again note as discussed above that the presently claimed invention (in its entirety) is fully supported under the requirements of 35 U.S.C. § 112, first paragraph, by the disclosure of prior application Serial No. 07/690,530 and is, therefore, entitled to an effective priority filing date of April 23, 1991. Since the cited Pouletty et al. reference was published one year after this effective priority filing date, Pouletty et al is not a valid reference herein for the purposes of 35 U.S.C. § 103. Applicants, therefore, respectfully request reconsideration and withdrawal of the outstanding rejection.

The New Matter Rejections under 35 U.S.C. § 112, First Paragraph

Claims 2 and 6 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. With regard to Claim 2, the Examiner asserts that there is no specification support for the recitation of "an antigen foreign to said mammalian host to which antibodies are present". With regard to Claim 6, the Examiner asserts that there is no specification support for the recitation of "low molecular weight binding molecule".

Without necessarily agreeing with the propriety of the outstanding rejection, Applicants have amended Claims 2 and 6 to remove the offending phrases, thereby obviating these rejections.

On the basis of the amendments and remarks presented herein, we believe that this application is now in condition for immediate allowance and respectfully request the Examiner to withdraw the outstanding rejections and pass this application to issue.

Respectfully submitted,

FLEHR HOHBACH TEST
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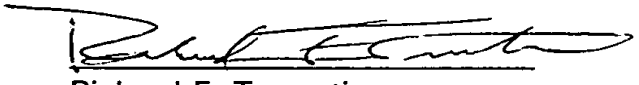

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